Walking pace is associated with lower risk of all-cause and cause-specific mortality

Running title - Walking pace, diseases risk and mortality

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ABSTRACT

Table 1. Cohort characteristics by walking pace

		Walking pace		
	Overall	**Slow (<3 miles.h^{-1})**	**Average (3-4 miles.h^{-1})**	**Brisk (>4 miles.h^{-1})**
Socio-demographics				
Total n	318,185	14,793	164,236	139,156
Sex (females), n(%)	174,006 (54.7)	8,483 (57.3)	89,847 (54.7)	75,676 (54.4)
Age (years), mean (SD)	56.0 (8.14)	58.2 (7.73)	56.8 (8.08)	54.9 (8.11)
Deprivation index tertile, n (%)				
Lower (Less deprived)	109,884 (34.5)	3,511 (23.7)	55,566 (33.8)	50,807 (36.5)
Middle	108,397 (34.1)	4,465 (30.2)	56,017 (34.1)	47,915 (34.4)
Higher (Most deprived)	99,904 (31.4)	6,817 (46.1)	52,653 (32.1)	40,434 (29.1)
Ethnicity				
Whites	302,067 (94.9)	13,090 (88.5)	154,468 (94.1)	134,509 (96.7)
Others/mixed	4,614 (1.5)	425 (2.9)	2,607 (1.6)	1,582 (1.1)
South Asians	5,655 (1.8)	721 (4.9)	3,595 (2.2)	1,339 (1.0)
Blacks	4,871 (1.5)	447 (3.0)	2,930 (1.8)	1,494 (1.1)
Chinese	978 (0.3)	110 (0.7)	636 (0.3)	232 (0.1)
Employment status				
Employed	193,277 (60.7)	5,521 (37.3)	94,593 (57.6)	93,163 (67.0)
Retired	102,224 (32.1)	6,238 (42.2)	58,070 (35.4)	37,916 (27.3)
Looking after home/family	9,524 (3.0)	476 (3.2)	4,905 (3.0)	4,143 (3.0)
Unable to work	5,588 (1.8)	2,090 (14.1)	2,572 (1.6)	926 (0.6)
Unemployed	5,133 (1.6)	352 (2.4)	2,899 (1.8)	1,882 (1.3)
Voluntary work	1,518 (0.5)	60 (0.4)	760 (0.4)	698 (0.5)
Student	921 (0.3)	56 (0.4)	437 (0.2)	428 (0.3)
Smoking status, n (%)				
Never	180,226 (56.6)	7,256 (49.1)	90,937 (55.4)	82,033 (59.0)
Previous	107,853 (33.9)	5,344 (36.1)	56,856 (34.6)	45,653 (32.8)
Current	30,106 (9.5)	2,193 (14.8)	16,443 (10.0)	11,470 (8.2)
Obesity-related markers				
BMI (kg.m^{-2}), mean (SD)	27.0 (4.50)	30.9 (6.26)	27.8 (4.55)	25.7 (3.71)
BMI Categories, n (%)				
Underweight (<18.5 kg.m^{-2})	1,594 (0.5)	51 (0.3)	549 (0.3)	994 (0.7)
Normal weight (18.5-24.9 kg.m^{-2})	111,470 (35.0)	2,309 (15.6)	45,855 (27.9)	63,306 (45.5)
Overweight (25.0 to 29.9 kg.m^{-2})	137,007 (43.1)	5,019 (33.9)	73,907 (45.0)	58,081 (41.7)
Obese (≥30.0 kg.m^{-2})	68,114 (21.4)	7,414 (50.2)	43,925 (26.8)	16,775 (12.1)
Waist Circumference (cm), mean (SD)	89.2 (13.0)	98.3 (14.9)	91.1 (12.9)	86.0 (11.9)
Central Obesity, n (%)	96,080 (30.2)	8,861 (59.9)	60,191 (36.7)	27,028 (19.4)
% Body fat, mean (SD)	30.9 (8.43)	36.0 (9.25)	32.1 (8.41)	28.9 (7.84)
Fitness and Physical activity				
Fitness (METs), mean (SD)	9.72 (2.77)	8.33 (2.48)	9.32 (2.67)	10.3 (2.79)
Grip strength (Kg), mean (SD)	31.1 (10.9)	26.4 (11.0)	30.5 (10.9)	32.3 (10.8)
Time spent walking (min.day^{-1}), mean (SD)	53.2 (56.2)	43.3 (50.0)	53.5 (57.3)	53.9 (55.5)
Moderate intensity PA (min.day^{-1}), mean (SD)	45.0 (54.8)	40.9 (52.0)	45.1 (55.1)	45.2 (54.7)
Vigorous intensity PA (min.day^{-1}), mean (SD)	21.1 (27.4)	18.8 (28.2)	20.3 (27.4)	22.1 (27.3)
Total PA (METs.min.week^{-1}), mean (SD)	2,860.7 (3,052.4)	2,053.6 (2,503.5)	2,774.4 (3,012.1)	3,048.4 (3,133.2)
Physical inactivity, n (%)	39,360 (17.1)	2,214 (25.5)	21,231 (18.3)	15,915 (15.2)
TV-viewing (h.day^{-1})	2.67 (1.49)	3.45 (1.96)	2.83 (1.49)	2.40 (1.37)
Dietary intakes				
Alcohol intake (% of TE), mean (SD)	5.27 (6.50)	4.30 (6.68)	5.14 (6.59)	5.47 (6.39)
Fruit & Vegetables intake (portion.day^{-1}), mean (SD)	338.4 (1.93.0)	328.8 (216.9)	327.4 (190.8)	352.4 (192.1)
Oily fish (portion.day^{-1}), mean (SD)	1.66 (0.92)	1.57 (0.98)	1.63 (0.92)	1.71 (0.92)

Processed meat intake (portion.day^{-1}), mean (SD)	1.84 (1.06)	1.97 (1.12)	1.91 (1.05)	1.76 (1.06)
Red meat intake (portion.day^{-1}), mean (SD)	2.08 (1.41)	2.23 (1.63)	2.13 (1.42)	2.00 (1.37)
Health status				
Diabetes, n (%)	12,449 (3.9)	1,771 (12.0)	7,665 (4.7)	3,013 (2.2)
Systolic blood pressure (mmHg), mean (SD)	137.6 (18.6)	140.3 (18.7)	138.9 (18.7)	135.9 (18.4)
CVD medication, n (%)	73,389 (23.1)	6,399 (43.2)	43,223 (26.3)	23,767 (17.1)
Health self-rating, n (%)				
Excellent	61,704 (19.4)	554 (3.8)	23,028 (14.0)	38,122 (27.4)
Good	194,547 (61.1)	5,374 (36.3)	103,870 (63.2)	85,303 (61.3)
Fair	54,972 (17.3)	6,224 (42.1)	34,116 (20.8)	14,632 (10.5)
Poor	6,962 (2.2)	2,641 (17.8)	3,222 (2.0)	1,099 (0.8)

BMI body mass index; PA physical activity; MET metabolic-equivalent; TE total energy. SD standard deviation; n number; CVD cardiovascular disease; COPD chronic obstructive pulmonary disease. * Fitness data was available for n=67,322 participants.

Purpose - Walking pace is associated with all-cause and cardiovascular disease (CVD) mortality. Whether this association extends to other health outcomes and whether it is independent of total amount of time walked are currently unknown. Therefore, the aim of this study was to investigate whether usual walking pace is associated with a range of health outcomes.

Methods – 318,185 UK Biobank participants (54% women) aged 40-69 years were included. Walking pace and total walking time were self-reported. The outcomes comprised: all-cause mortality as well as incidence and mortality from cardiovascular disease (CVD), respiratory disease and cancer. The associations were investigated using Cox proportional hazard models.

Results - Over a mean of 5.0 years [ranging from 3.3 to 7.8], 5,890 participants died, 18,568 developed CVD, 5,430 respiratory disease and 19,234 cancer. In a fully adjusted model, compared to slow pace walkers, men and women, respectively, with a brisk pace having lower risk of mortality from all-causes (HR0.79 [95% CI: 0.69; 0.90] and 0.73 [95% CI: 0.62; 0.85]), CVD (HR 0.62 [0.50; 0.76] and 0.80 [0.73; 0.88]), respiratory disease (HR 0.58 [95% CI 0.43; 0.78] and 0.66 [0.57; 0.77]), COPD (HR 0.26 [95% 0.12; 0.56] and 0.28 [0.16; 0.49]). No associations were found for all-cause cancer, colorectal, breast cancer. However, brisk walking was associated with a higher risk of prostate cancer.

Conclusions: Walking pace is associated with lower risk of a wide range of important health conditions, independently of overall time spent walking.

Keywords: Mortality; cardiovascular, cancer, walking, walking pace, UK biobank

Introduction

Current physical activity guidelines recommend at least 150 minutes of moderate intensity, or 75 minutes high intensity, physical activity per week for all adults [1]. However, around one third of the adult population worldwide do not meet these recommendations [2]. This observation highlights the difficulty many people have incorporating physical activity recommendations into their daily lives in a sustainable way [3]. Lack of time is frequently cited as the primary barrier to meeting the current recommendations [4].

Walking is the most common form of physical activity that adults perform, and is acceptable and accessible to almost the entire population [5]. A meta-analysis of randomised controlled trials found that increased walking time led to increased fitness and decreased body weight, body mass index (BMI), percentage body fat and systolic blood pressure in adults [6]; all well known risk factors for premature mortality and morbidity [7]. Previous smaller studies, mostly conducted on older adults, found an inverse association between objectively assessed walking pace and all-cause mortality [8-10]. Recent analysis of UK Biobank data found that self-reported walking pace was strongly associated with both all-cause and CVD mortality; indeed the risk associated with walking at <3 miles per hour, compared with ≥4 miles per hour, was stronger than for smoking [7, 11]. However these previous studies did not investigate whether the associations with walking pace vary with, and are independent of, time spent walking or whether dose response relationships are present. Furthermore, they did not investigate associations of walking pace with a wider range of health outcomes, such as respiratory disease and cancer sub-types. Therefore, the aim of this study was to investigate, in a large, prospective population-based cohort of middle age and older adults, the associations between usual walking pace and a range of cardiovascular, respiratory and cancer health outcomes. A secondary aim

was to explore whether there were dose relationships or threshold effects, and whether the associations varied with, and were independent of, total time spent walking.

METHODS

Between April 2007 and December 2010, UK Biobank recruited 502,628 participants (5.5% response rate), aged 40-69 years from the general population [12-15]. However, only 318,185 with full data available were included in this study. Participants attended one of 22 assessment centres across England, Wales and Scotland [12-15] where they completed a touch-screen questionnaire, had physical measurements taken and provided biological samples, as described in detail elsewhere [12-15]. All-cause mortality and CVD, respiratory disease, chronic obstructive pulmonary disease (COPD) and cancer mortality and incidence were the main outcomes; and walking pace (slow, average and brisk) was the exposure of interest. Sociodemographic factors (age, sex, ethnicity, employment status and area-based deprivation), lifestyle factors (smoking status, self-reported discretionary screen time, total physical activity, grip strength and dietary intake), health related parameters (systolic blood pressure, diabetes, medication for CVD, and self-reported health rating), body mass index and month of recruitment were treated as potential confounders. To minimise potential reverse causality, i.e. those that are less well are not able to walk as fast, all analyses were conducted using landmark analysis excluding events occurring in the first 2 years of follow-up. Furthermore participants with baseline medical diagnoses of depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson's disease, dementia, chronic pain syndrome, heart diseases, diabetes and cancer were excluded (n= 71,026). Those who reported being unable to walk (n=1,929) or those who did not answer these questions were also excluded from the study (n=7,669).

Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Date and cause of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and to the Scottish Morbidity Records (SMR01) (Scotland). Detailed information regarding the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. At the time of analysis, mortality data were available up to 31 January 2016. Mortality analysis was therefore censored at these dates or date of death if this occurred earlier. Hospital admission data were available until 31 March 2015, resulting in disease specific analyses being censored at this date, or the date of hospital admission or death if these occurred earlier. Follow-up information on cancer was obtained via linkage to three routine administrative databases, death certificates, hospital admissions and cancer registrations, with complete follow-up available until 31 March 2015. Incident CVD was defined as a hospital admission or death with ICD10 code I60, I61, I63, I64, I21, I21.4 or I21.9; respiratory disease was defined as ICD10 code J09-J98 or I26-I27 and chronic obstructive pulmonary disease (COPD) was defined as ICD10 code J44. All-cause cancer was defined as an ICD code of C0.0-C9.9, D3.7-9 or D4.0-8. Cause-specific cancers were defined using the following ICD10 codes: breast cancer (C50), prostate cancer (C61), lung cancer (C34) and colorectal cancer (C18, C19 and C20).

Walking pace was self-reported using a touch-screen questionnaire completed at the baseline visit. The participants who indicated they were able to walk were asked "How would you describe your usual walking pace?" and they could choose one of the following: slow pace defined as <3 miles per hour; average pace defined as 3-4 miles per hour; and brisk pace defined as >4 miles per hour. Physical activity was based on self-report, using the IPAQ short form, and total physical activity was computed as the sum of walking, moderate and vigorous

activity, measured as metabolic equivalents (MET-hours.week^{-1}) [16]. A proxy measure of total discretionary time spent in screen-related behaviours (TV-viewing and PC-screen) was calculated. Participants were asked "In a typical day, how many hours do you spend watching TV, doing PC screening or driving during your leisure time?", and this combined figure was used as a proxy for discretionary sedentary measure (expressed as hours per week). Age- and sex-specific walking categories were derived from total walking minutes (from IPAQ) per day (cut-off points are presented in Supplementary Table 1). Grip strength was assessed using a Jamar J00105 hydraulic hand dynamometer and the mean of the three measurements for each hand were used, grip strength was expressed as kg [17]. Fitness was measured in a subset of the cohort (n=67,700) using a previously validated 6-minute incremental ramp cycle ergometer test, as described previously [18].

Dietary information was collected via the Oxford WebQ; a web-based 24-hour recall questionnaire which was developed specifically for use in large population studies [19, 20]. Area-based socioeconomic status was derived from postcode of residence, using the Townsend score [21]. Age was calculated from dates of birth and baseline assessment. Smoking status was self-reported as never, former or current smoking. Employment status, self-health rating (excellent, good, average and bad) was self-reported. Medical history (physician diagnosis of illness) was collected using the self-completed, baseline questionnaire. Height and body weight were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as (weight/height^2) and the WHO criteria applied to classify BMI into: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m^{-2} [22]. Waist circumference was used to derive central obesity: ≥88 cm for women and ≥102 cm for men [22]. Body composition (body fat and fat free mass) were measured using bio-impedance (Tanita BC418MA) by trained nurses. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

The associations between walking pace and health outcomes were investigated using separate Cox-proportional hazard models using slow walking pace as the reference group. Results are reported as hazard ratios, together with 95% confidence intervals. A hazard ratio for trend was estimated by fitting walking pace as ordinal variable into the model (0=slow pace, 1=average pace and 3=brisk pace), the trend hazard ratio indicate the hazard equivalent to moving one category up in walking pace. The models for disease specific outcomes were conducted excluding participants with the relevant disease at baseline (as mentioned earlier). Moreover, we excluded from all analysis individuals who reported comorbidities which could affect walking pace and time spent walking or those with missing data and those who reported being unable to walk were excluded from the analyses.

For each outcome, we ran three models included an increasing number of covariates: Model 1 - included month of recruitment and sociodemographic covariates (age, sex, ethnicity, deprivation index and employment status); Model 2 - was also adjusted for systolic blood pressure, medication for CVD, self-health rating and BMI categories; and Model 3 - was also adjusted for smoking, discretionary screen time, dietary intake (alcohol, red meat, processed meat, oily fish, processed meat and fruit and vegetables), handgrip strength and total physical activity (this variable was replaced by moderate-to-vigorous physical activity when the interaction between walking pace and walking time tertiles was investigated).

Tertiles of time spent walking daily were derived for age, sex strata (see Table, Supplemental Digital Content 1, age- and sex-specific cut-offs). To investigate whether the association between walking pace and health outcomes differed by time spent walking, a multiplicative

interaction term between walking pace and walking tertiles was fitted into our models for each outcome.

The proportional hazards assumption was checked by tests based on Schoenfeld residuals. All analyses were performed using STATA 14 statistical software (StataCorp LP).

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study.

Results

The 2-year landmark analyses and exclusion of individuals with major comorbidities at baseline meant 318,185 participants were included in the analyses. The mean follow-up period for all-cause and cause-specific mortality was 5.0 years [ranging from 3.3 to 7.8] and 4.1 years [ranging from 2.4 to 7.0] for cause-specific incidence. Over the follow-up period, 18,568 (5.8%) participants developed CVD, 5,430 (1.7%) respiratory disease and 19,234 (6.0%) cancer, and 5,890 (1.9%) participants died (1,761 (0.6%) from CVD, 878 (0.3%) from respiratory disease and 3,687 (1.2%) from cancer.

The characteristics of participants by walking pace category are summarised in Table 1. Compared with individuals who walked slowly, brisk walkers were less deprived and had a lower prevalence of smoking and obesity. They had lower BMI, waist circumference and percentage body fat, and lower intake of processed and red meat, but higher intake of alcohol,

oily fish, fruit and vegetables. They also had higher levels of physical activity, fitness and muscle strength and lower levels of discretionary screen time (Table 1). The cohort characteristics stratified by sex are presented (see Table, Supplemental Digital Content 2, baseline characteristics by walking pace in women and Table, Supplemental Digital Content 3, baseline characteristics by walking pace in men).

Overall, our analyses taking detailed account of the above confounders, suggest that both average and brisk walking pace were associated with a lower hazard for all-cause, CVD, respiratory disease and COPD mortality in both men and women, compared to slow walking pace (Figure 1). The hazard ratios for health outcomes mortality, both minimally and fully adjusted, are presented (see Table, Supplemental Digital Content 4, walking pace and mortality in women, and Table, Supplemental Digital Content 5, walking pace and mortality in men). In summary, the fully adjusted hazard per one category increment in walking pace was 0.91 [95% CI: 0.85; 0.98] and 0.90 [95% CI: 0.85; 0.95], for all-cause mortality in women and men, respectively. The magnitude of the association was stronger for CVD (Women 0.71 [95% CI: 0.61; 0.83]; Men 0.81 [95% CI: 0.73; 0.90]), respiratory (Women 0.72 [95% CI: 0.58; 0.89]; Men 0.76 [95% CI: 0.66; 0.88]), and COPD (Women 0.19 [95% CI: 0.08; 0.45]; Men 0.49 [95% CI: 0.33; 0.73]), compared to all-cause mortality per one category increment in walking pace, as shown in Figure 1).

Similar results were observed for cause-specific incidence, except for prostate cancer for a higher hazard was observed in those reporting either average or brisk walking pace (Figure 2). The hazard ratios for health outcomes incidence, both minimally and fully adjusted, are presented (see Table, Supplemental Digital Content 6, walking pace and incidence in women, and Table, Supplemental Digital Content 7, walking pace and incidence in men). In our fully

adjusted model, the hazards per one category increment in walking pace were 0.92 [95% CI: 0.88; 0.96] and 0.94 [95% CI: 0.91; 0.97], for CVD incidence in women and men, respectively. Similar trend swere observed for all-respiratory disease incidence (Women 0.84 [95% CI: 0.78; 0.90]; Men 0.84 [95% CI: 0.79; 0.89]), and COPD (Women 0.54 [95% CI: 0.42; 0.70]; Men 0.60 [95% CI: 0.48; 0.74]) per one category increment in walking pace, as shown in figure 2. However, the hazard for prostate cancer risk was 1.10 [95% CI: 1.02; 1.19]) per one category increment in walking pace.

When the associations between walking pace and health outcomes were stratified by walking time tertiles (expressed as $min.day^{-1}$), significant interactions were found for all-cause mortality but not for CVD, respiratory disease, and all-cancer incidence and mortality (Figure 3 and 4 and see Table, Supplemental Digital Content 8, walking pace tertiles and mortality in women, and Table, Supplemental Digital Content 9, walking pace tertiles and mortality in men)). Our findings show that, compared to those reporting brisk walking pace and who were classified in the higher walking time category, individuals who reported slow walking pace were at higher risk for all-cause mortality if they were classified in the middle or lower walking time categories. However, for CVD and respiratory incidence and mortality, those who reported a slow pace were at higher risk for these health outcomes regardless if they were classified in the higher, middle or lower walking time categories. Interestingly, those who were in the middle or lower walking time tertiles were not at higher risk for these outcomes if they reported brisk walking pace (Figure 3 and 4). These trends were not observed for cancer mortality or incidence. All these findings were independent of major confounding factors.

DISCUSSION

Usual walking pace was associated with a range of health outcomes that extended beyond CVD and all-cause mortality, to all-respiratory diseases and COPD in both men and women. The associations demonstrated were independent of measured confounders; most notably total physical activity. Our findings also show that those reporting normally walking at a slow pace had higher hazard for all-cause mortality and CVD and respiratory incident and mortality regardless the time spent walking. Future research, with appropriately designed randomised-controlled trials, is needed to determine if the current observations reflect a causal association and if so these findings could have import implications for physical activity recommendations.

Comparison with previous studies

The current finding of an inverse association between self-reported usual walking pace and all-cause and CVD mortality is consistent with previous studies [8, 23-31]. The majority of these previous studies have, however, been carried out in older people and looked at maximal walking pace [23, 24, 31-33] making the findings less relevant for the general population. Previous studies carried out over a wider age range have generally been small or modest in size (1,255 – 38,981 participants) [9, 25, 26, 30] and have involved studies of recreational walkers [25] and CVD patients [26, 30]. Two recent studies by Yates et al.,[11] and Ganna and Ingelsson [7], using UK Biobank data found that walking pace was a stronger predictor of all-cause and CVD mortality, indicating that this measure, that can be simply obtained by verbal interviews without physical examination, is a stronger predictor of mortality. The current study, in a well characterised and large cohort, confirms that a slow walking pace is associated with an increased all-cause and CVD mortality and extends these findings with novel data to demonstrate that an average (3-4 miles.hour^{-1}) or brisk walking pace (>4 miles.hour^{-1}) is associated with a lower risk of COPD and all-cancer mortality whilst a brisk walking pace is associated with a lower risk of lung cancer mortality and incidence. Surprisingly an average

and brisk walking pace were also associated with an increased risk of prostate cancer incidence, but not mortality. Previously positive associations between prostate cancer incidence and physical activity (or fitness a surrogate of total physical activity) has been reported in some [34, 35] but not all [36] studies. The exact reasons behind these observations are unknown, but differences in health-seeking behaviours, may be a contributing factor [34]. For example, it has been postulated that health-conscious men (who are more likely to walk briskly), may be more likely to attend screening or report symptoms leading to increased detection of early cancers and improved prognosis [34].

We have extended the findings that slow walking pace is associated with increased risk of poor health outcomes by also demonstrating, that this association is present regardless of the amount of total time spent walking. Not only were those reporting a slow walking pace at higher risk for all-cause, CVD and respiratory incidence and mortality compared to those reporting brisk walking pace but the incidence and mortality risk was the same in those reporting brisk walking across all three walking time categories. Taken together, this indicates that the pace at which walking is habitually carried out maybe more important for health outcomes than the total amount of time spent walking, although it is worth pointing out that whilst we have carried out robust statistical adjustment here we cannot rule out reverse causality (i.e. those that are less well are not able to walk as fast) even though we tried to minimise this in our landmark analyses and by taking out all individuals with long standing illness. These findings are, however, similar to those reported in the Caerphilly study where only leisure activity classified as heavy or vigorous was associated with a reduced risk of CVD mortality [37], although this study was confined to middle-aged men and included all forms of activity, with the current study focused on walking only. Appropriately designed randomised controlled trials are needed to determine if these findings are causal.

Implications of findings

Walking is frequently recommended as a tool to increase physical activity levels as it is free and generally accessible to all, but currently the primary focus has been to increase the time spent or the number of steps walked [38, 39] with the pace of walking often receiving less focus. If future trials confirm the findings of the current study this may indicate that whilst strategies to increase total walking time, which is currently the primary focus, will be of benefit it may be prudent to also ensure promotion of a brisk walking pace, where the individual is capable, to further enhance the benefits of walking. On the other hand, if these findings are shown not to be causal, the data indicates that self-reported walking pace may be a useful tool too indicate sub-clinical illness which may progress to poorer health outcomes.

Strengths and limitations

The UK Biobank is reasonably representative of the general population in terms of age, sex, ethnicity and socioeconomic status but is unrepresentative in terms of lifestyle [40]. Therefore, caution is needed in generalising summary statistics to the general population, but estimates of the magnitude of the associations are, nevertheless, generalisable. Participants were more likely to be older, to be women, and to live in less socioeconomically deprived areas; were less likely to be obese, to smoke, or to drink alcohol on a daily basis; and had fewer self-reported health outcomes. Rates of all-cause mortality and incidence of cancer were also lower.[41, 42]. This does not detract from the ability to generalize estimates of the magnitude of associations. Our study benefited from a very large number of participants, recruited from the general population, across the whole of the UK. We had sufficient power to undertake subgroup analyses by sex, which overcomes limitations from previous evidence. Reverse causality is possible in any observational study; however, when participants with existing disease diagnosed at baseline were removed from the analysis the associations remained significant. Moreover, our results

were broadly similar after a landmark analysis was conducted removing all events that occurred within the first two years of follow up. Walking pace was self-reported and, to our knowledge, the question used has not previously been validated. Although prevalent disease and comorbidities at baseline were self-reported, these self-reports were of physician diagnosed disease.

In conclusion, the current data has demonstrated that, irrespective of total walking time, a faster walking pace is associated with lower risk of a wide range of health outcomes. The findings require determination of causality in appropriately designed trials, but could have important implications for physical activity recommendations. They tentatively imply guidelines should encourage people to increase their walking pace (if low to begin with), rather than simply focusing on total time spent walking. As lack of time is the most commonly cited barrier to increasing activity levels; brisk walking of shorter duration may be easier to accommodate into busy schedules and the benefits may be greatest among those failing to meet the current recommendations.

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falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by ACSM.

AUTHOR CONTRIBUTIONS

CCM, SG, FP, JPP, NS, JMRG contributed to the conception and design of the study, advised on all statistical aspects and interpreted the data. CCM, SG and FP performed the statistical analyses. CCM, SG, FP, JMRG, JPP and NS drafted the manuscript. All authors reviewed the manuscript and approved the final version to be published. CCM, SG, JPP, NS and JMRG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPLEMENTAL DIGITAL CONTENT

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Supplemental Digital Content 2.docx

Supplemental Digital Content 3.docx

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FIGURE LEGENDS

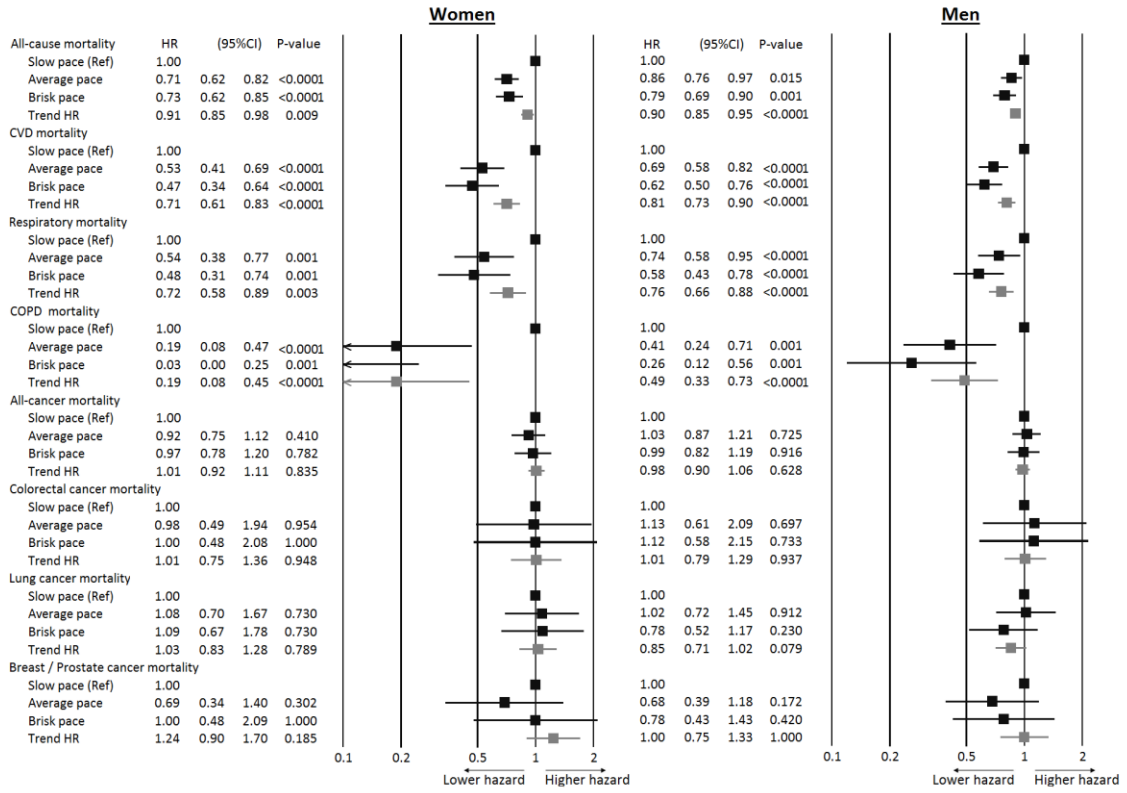


Figure 1. Cox proportional hazard models of the association between walking pace and all- and cause-specific mortality by sex.

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by walking pace category. Slow walking pace was used as reference group for these analysis. Trend hazard ratio indicate the change in the hazard per one category change in walking pace. All analyses were conducted using a 2-years landmark analyses and by excluding participants with major diseases at baseline. Analyses were adjusted for month of recruitment, age, deprivation index, employment status, ethnicity, systolic blood pressure, medication for CVD, self-health rating, BMI categories, smoking, discretionary screen time, dietary intake (alcohol, red meat, processed meat, oily fish, processed meat and fruit and vegetables), handgrip strength and total physical activity.

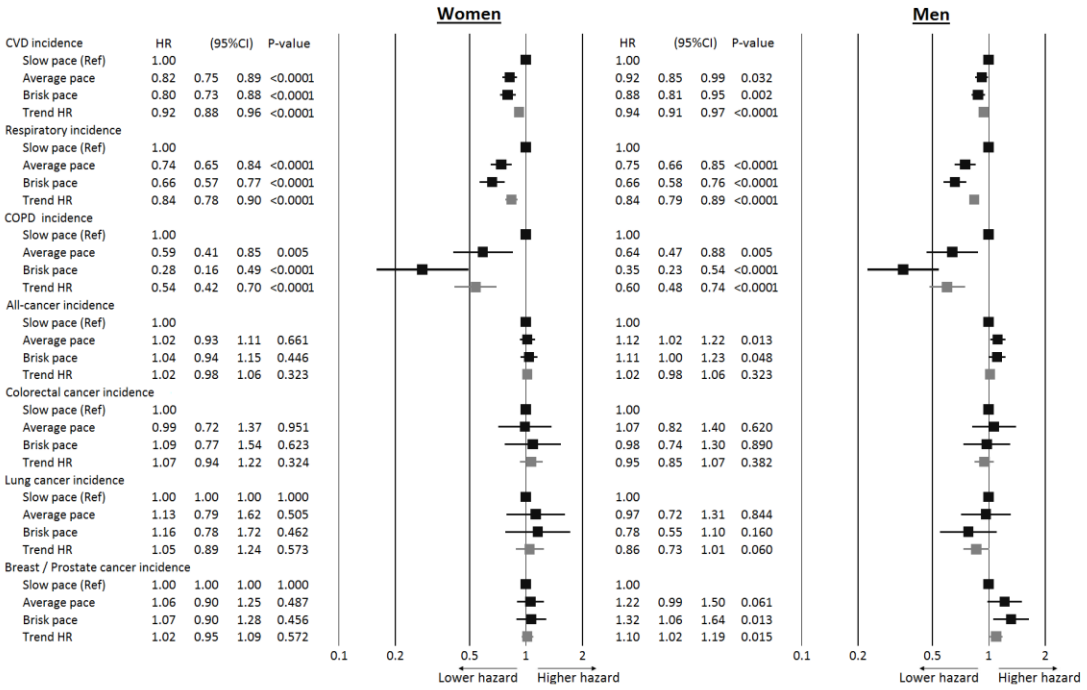
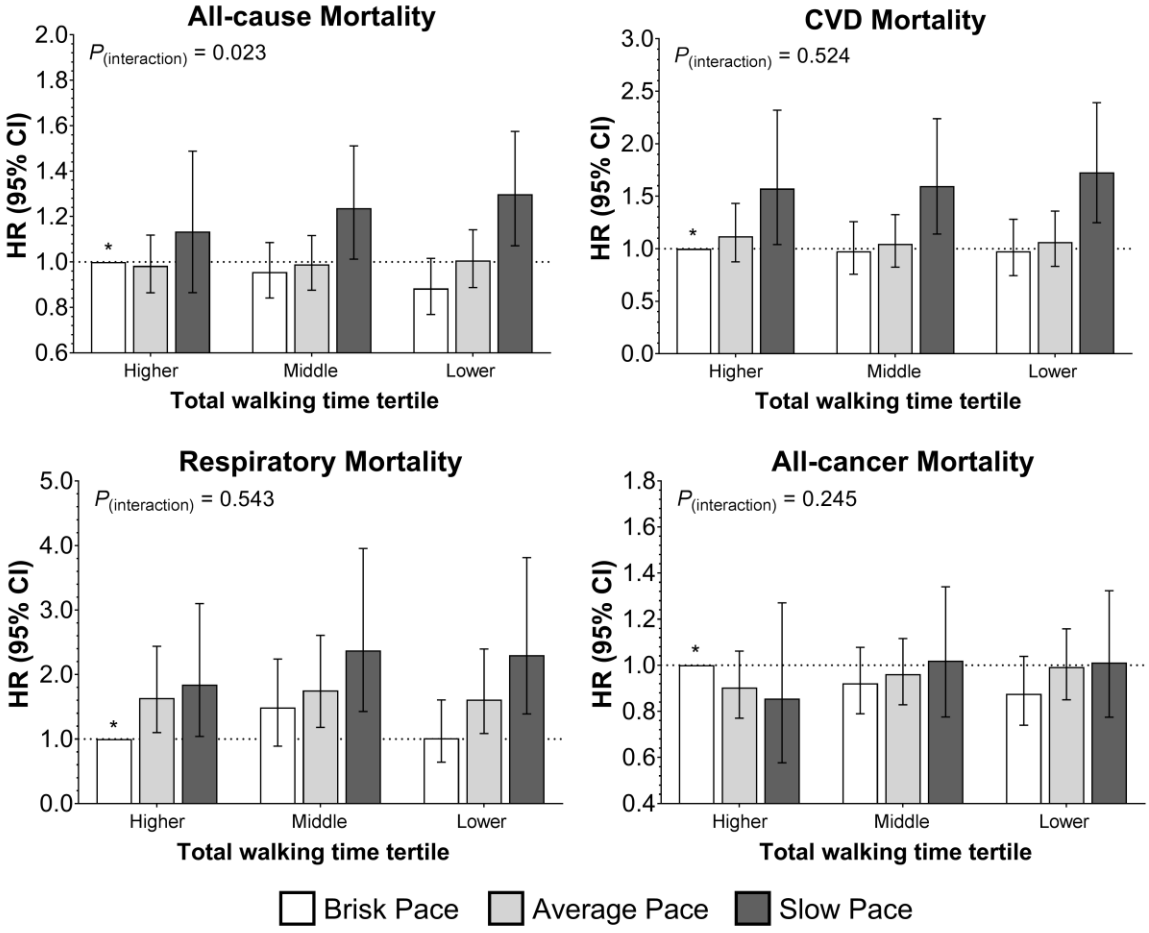


Figure 2. Cox proportional hazard models of the association between walking pace and cause-specific incidence by sex.

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by walking pace category. Slow walking pace was used as reference group for these analysis. Trend hazard ratio indicate the change in the hazard per one category change in walking pace. All analyses were conducted using a 2-years landmark analyses and by excluding participants with major diseases at baseline. Analyses were adjusted for month of recruitment, age, deprivation index, employment status, ethnicity, systolic blood pressure, medication for CVD, self-health rating, BMI categories, smoking, discretionary screen time, dietary intake (alcohol, red meat, processed meat, oily fish, processed meat and fruit and vegetables), handgrip strength and total physical activity.



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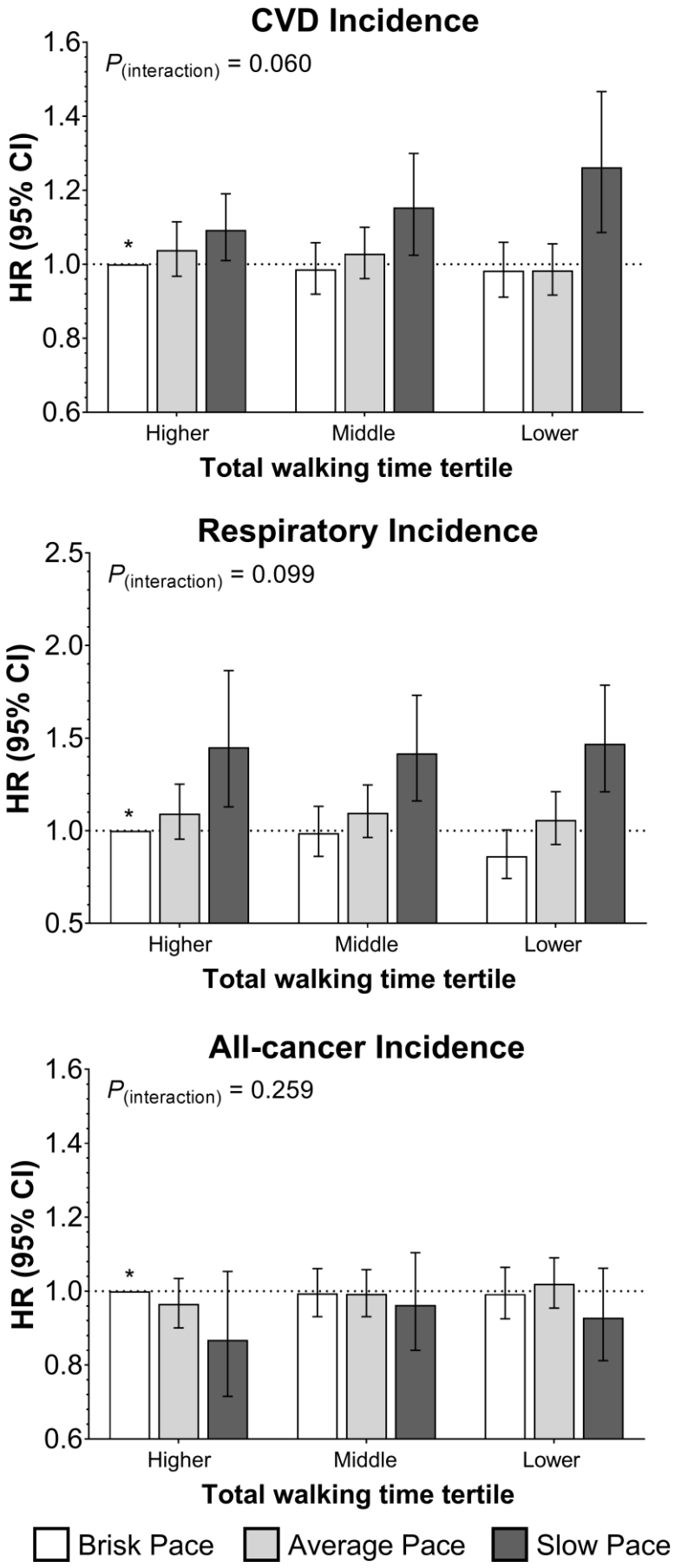
515 **Figure 3. Hazard ratio for all- and cause-specific mortality by walking pace and total**
516 **walking time tertiles**

517 Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by
518 walking pace and total walking time tertiles. Individuals who reported brisk walking pace and
519 higher levels of walking time were used as reference group. Analyses were conducted using a
520 2 years-landmark analyses and all participants with comorbidities at baseline were excluded
521 from the analyses. The analyses were adjusted for month of recruitment, age, deprivation index,
522 employment status, ethnicity, systolic blood pressure, medication for CVD, self-health rating,
523 BMI categories, smoking, discretionary screen time, dietary intake (alcohol, red meat,
524 processed meat, oily fish, processed meat and fruit and vegetables), handgrip strength and
525 moderate to vigorous physical activity.


CVD Incidence
$P_{(interaction)}$ = 0.060
HR (95% CI)
1.6
1.4
1.2
1.0
0.8
0.6
*
Higher
Middle
Lower
Total walking time tertile
Respiratory Incidence
$P_{(interaction)}$ = 0.099
HR (95% CI)
2.5
2.0
1.5
1.0
0.5
*
Higher
Middle
Lower
Total walking time tertile
All-cancer Incidence
$P_{(interaction)}$ = 0.259
HR (95% CI)
1.6
1.4
1.2
1.0
0.8
0.6
*
Higher
Middle
Lower
Total walking time tertile
Brisk Pace
Average Pace
Slow Pace

526

Figure 4. Hazard ratio for cause-specific incidence by walking pace and total walking time tertiles

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by walking pace and total walking time tertiles. Individuals who reported brisk walking pace and higher levels of walking time were used as reference group. Analyses were conducted using a 2 years-landmark analyses and all participants with comorbidities at baseline were excluded from the analyses. The analyses were adjusted for month of recruitment, age, deprivation index, employment status, ethnicity, systolic blood pressure, medication for CVD, self-health rating, BMI categories, smoking, discretionary screen time, dietary intake (alcohol, red meat, processed meat, oily fish, processed meat and fruit and vegetables), handgrip strength and moderate to vigorous physical activity.

Table 1. Cohort characteristics by walking pace

		Walking pace		
	Overall	**Slow (<3 miles.h^{-1})**	**Average (3-4 miles.h^{-1})**	**Brisk (>4 miles.h^{-1})**
Socio-demographics				
Total n	318,185	14,793	164,236	139,156
Sex (females), n(%)	174,006 (54.7)	8,483 (57.3)	89,847 (54.7)	75,676 (54.4)
Age (years), mean (SD)	56.0 (8.14)	58.2 (7.73)	56.8 (8.08)	54.9 (8.11)
Deprivation index tertile, n (%)				
Lower (Less deprived)	109,884 (34.5)	3,511 (23.7)	55,566 (33.8)	50,807 (36.5)
Middle	108,397 (34.1)	4,465 (30.2)	56,017 (34.1)	47,915 (34.4)
Higher (Most deprived)	99,904 (31.4)	6,817 (46.1)	52,653 (32.1)	40,434 (29.1)
Ethnicity				
Whites	302,067 (94.9)	13,090 (88.5)	154,468 (94.1)	134,509 (96.7)
Others/mixed	4,614 (1.5)	425 (2.9)	2,607 (1.6)	1,582 (1.1)
South Asians	5,655 (1.8)	721 (4.9)	3,595 (2.2)	1,339 (1.0)
Blacks	4,871 (1.5)	447 (3.0)	2,930 (1.8)	1,494 (1.1)
Chinese	978 (0.3)	110 (0.7)	636 (0.3)	232 (0.1)
Employment status				
Employed	193,277 (60.7)	5,521 (37.3)	94,593 (57.6)	93,163 (67.0)
Retired	102,224 (32.1)	6,238 (42.2)	58,070 (35.4)	37,916 (27.3)
Looking after home/family	9,524 (3.0)	476 (3.2)	4,905 (3.0)	4,143 (3.0)
Unable to work	5,588 (1.8)	2,090 (14.1)	2,572 (1.6)	926 (0.6)
Unemployed	5,133 (1.6)	352 (2.4)	2,899 (1.8)	1,882 (1.3)
Voluntary work	1,518 (0.5)	60 (0.4)	760 (0.4)	698 (0.5)
Student	921 (0.3)	56 (0.4)	437 (0.2)	428 (0.3)
Smoking status, n (%)				
Never	180,226 (56.6)	7,256 (49.1)	90,937 (55.4)	82,033 (59.0)
Previous	107,853 (33.9)	5,344 (36.1)	56,856 (34.6)	45,653 (32.8)
Current	30,106 (9.5)	2,193 (14.8)	16,443 (10.0)	11,470 (8.2)
Obesity-related markers				
BMI (kg.m^{-2}), mean (SD)	27.0 (4.50)	30.9 (6.26)	27.8 (4.55)	25.7 (3.71)
BMI Categories, n (%)				
Underweight (<18.5 kg.m^{-2})	1,594 (0.5)	51 (0.3)	549 (0.3)	994 (0.7)
Normal weight (18.5-24.9 kg.m^{-2})	111,470 (35.0)	2,309 (15.6)	45,855 (27.9)	63,306 (45.5)
Overweight (25.0 to 29.9 kg.m^{-2})	137,007 (43.1)	5,019 (33.9)	73,907 (45.0)	58,081 (41.7)
Obese (≥30.0 kg.m^{-2})	68,114 (21.4)	7,414 (50.2)	43,925 (26.8)	16,775 (12.1)
Waist Circumference (cm), mean (SD)	89.2 (13.0)	98.3 (14.9)	91.1 (12.9)	86.0 (11.9)
Central Obesity, n (%)	96,080 (30.2)	8,861 (59.9)	60,191 (36.7)	27,028 (19.4)
% Body fat, mean (SD)	30.9 (8.43)	36.0 (9.25)	32.1 (8.41)	28.9 (7.84)
Fitness and Physical activity				
Fitness (METs), mean (SD)	9.72 (2.77)	8.33 (2.48)	9.32 (2.67)	10.3 (2.79)
Grip strength (Kg), mean (SD)	31.1 (10.9)	26.4 (11.0)	30.5 (10.9)	32.3 (10.8)
Time spent walking (min.day^{-1}), mean (SD)	53.2 (56.2)	43.3 (50.0)	53.5 (57.3)	53.9 (55.5)
Moderate intensity PA (min.day^{-1}), mean (SD)	45.0 (54.8)	40.9 (52.0)	45.1 (55.1)	45.2 (54.7)
Vigorous intensity PA (min.day^{-1}), mean (SD)	21.1 (27.4)	18.8 (28.2)	20.3 (27.4)	22.1 (27.3)
Total PA (METs.min.week^{-1}), mean (SD)	2,860.7 (3,052.4)	2,053.6 (2,503.5)	2,774.4 (3,012.1)	3,048.4 (3,133.2)
Physical inactivity, n (%)	39,360 (17.1)	2,214 (25.5)	21,231 (18.3)	15,915 (15.2)
TV-viewing (h.day^{-1})	2.67 (1.49)	3.45 (1.96)	2.83 (1.49)	2.40 (1.37)
Dietary intakes				
Alcohol intake (% of TE), mean (SD)	5.27 (6.50)	4.30 (6.68)	5.14 (6.59)	5.47 (6.39)
Fruit & Vegetables intake (portion.day^{-1}), mean (SD)	338.4 (1.93.0)	328.8 (216.9)	327.4 (190.8)	352.4 (192.1)
Oily fish (portion.day^{-1}), mean (SD)	1.66 (0.92)	1.57 (0.98)	1.63 (0.92)	1.71 (0.92)

Processed meat intake (portion.day^{-1}), mean (SD)	1.84 (1.06)	1.97 (1.12)	1.91 (1.05)	1.76 (1.06)
Red meat intake (portion.day^{-1}), mean (SD)	2.08 (1.41)	2.23 (1.63)	2.13 (1.42)	2.00 (1.37)
Health status				
Diabetes, n (%)	12,449 (3.9)	1,771 (12.0)	7,665 (4.7)	3,013 (2.2)
Systolic blood pressure (mmHg), mean (SD)	137.6 (18.6)	140.3 (18.7)	138.9 (18.7)	135.9 (18.4)
CVD medication, n (%)	73,389 (23.1)	6,399 (43.2)	43,223 (26.3)	23,767 (17.1)
Health self-rating, n (%)				
Excellent	61,704 (19.4)	554 (3.8)	23,028 (14.0)	38,122 (27.4)
Good	194,547 (61.1)	5,374 (36.3)	103,870 (63.2)	85,303 (61.3)
Fair	54,972 (17.3)	6,224 (42.1)	34,116 (20.8)	14,632 (10.5)
Poor	6,962 (2.2)	2,641 (17.8)	3,222 (2.0)	1,099 (0.8)

BMI body mass index; PA physical activity; MET metabolic-equivalent; TE total energy. SD standard deviation; n number; CVD cardiovascular disease; COPD chronic obstructive pulmonary disease. * Fitness data was available for n=67,322 participants.